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Review

Consensus statement on insulin therapy in chronic kidney disease

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ABSTRACT

Introduction: Diabetes mellitus (DM) is one of the leading causes of chronic kidney disease (CKD) which eventually leads to insulin resistance and decreased insulin degradation. In patients with diabetic kidney disease (DKD), the overall insulin requirement declines which necessitates the reassessment for individualization, adjustment and titration of insulin doses depending on the severity of kidney disease.

Objective: To provide simple and easily implementable guidelines to primary care physicians on appropriate insulin dosing and titration of various insulin regimens in patients with DKD.

Methods: Each insulin regimen (basal, prandial, premix and basal-bolus) was presented and evaluated for dosing and titration based on data from approved medical literatures on chronic kidney disease. These evaluations were then factored into the national context based on the expert committee representatives' and key opinion leaders' clinical experience and common therapeutic practices followed in India.

Results: Recommendations based on dosing and titration of insulins has been developed. Moreover, the consensus group also recommended the strategy for dose estimation of insulin, optimal glycaemic targets and self-monitoring in patients with DKD.

Conclusion: The consensus based recommendations will be a useful reference tool for health care practitioners to initiate, optimise and intensify insulin therapy in patients with DKD.

Contents

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1. Introduction

The increasing prevalence of diabetes mellitus (DM) is recognized as a leading cause of chronic renal failure (CRF) and end stage renal disease (ESRD) [1,2]. A region wise report published by Rajapurkar et al. in Indian population indicates that diabetic nephropathy was a preeminent cause of chronic kidney disease (CKD) with prevalence of 31.3%, 31.2%, 32.9% and 29.2% in East, North, South and West zones respectively. Further, this study observed that, out of total nephropathy patients, 1.7%, 4.2%, 20.2%, 27.2% and 47.3% were of CKD 1, 2, 3, 4 and 5 stages, respectively [3]. In a recent study by Prasanna Kumar et al., nearly 40% of diabetes patients suffer from moderate to severe CKD (having reduced estimated glomerular filtration rate [eGFR]) with a potential to advancement to ESRD. Renal dysfunction was present in 22.60% and 34.5% of diabetes population as per eGFR criteria (<60 mL/min/1.73 m^2) and urine albumin-to-creatinine ratio (UACR) criteria (≥30 mg/g) respectively [4].

Glomerular filtration rate (GFR) measures the level of kidney function and determine different stages of kidney disease. However, it has few limitations like interpretation of plasma creatinine alone and inaccuracy in measuring 24-h urine creatinine clearance [5]. Cockcroft and Gault published an equation based on age, weight, height and plasma creatinine, along with the correction factors to estimate the creatinine clearance [6]. The Australasian creatinine consensus working group recommended eGFR calculation based on the abbreviated Modification of Diet in Renal Disease (MDRD) formula [7]. Unlike Cockcroft and Gault's equation, there was lack of requirement for either body weight or height in this equation; thereby making it the most preferred equation. Furthermore, this equation was originally derived for CKD patients and was also validated in patients with diabetic kidney disease (DKD) and renal transplant recipients [5]. More recently, in 2009, the CKD Epidemiology Collaboration group (CKD-EPI) established a new equation which offered greater accuracy at higher GFR values and minimised the overdiagnosis of CKD with the MDRD equation [8]. The CKD-EPI equation was as accurate as MDRD based formula in patients with eGFR < 60 mL/min/1.73 m^2 and noticeably more exact in the subgroup with eGFR > 60 mL/min/1.73 m^2 [5].

In non-diabetes individual, 40–50% of insulin secreted by the pancreas is extracted through liver during its first passage. The remainder is degraded, to a lesser extent, in kidney, muscle and most other tissues. Of the total renal insulin clearance, 60% clearance occurs by glomerular filtration and 40% is extracted from peritubular vessels [9]. The endogenous insulin has a shorter mean plasma half-life (3–5 min), is not bound to plasma proteins and cleared from the circulation within 10–15 min [10,11].

Most of the oral antidiabetic agents have limitations, either because of dose adjustment or safety reasons, in renal insufficiency; thereby resulting in higher tendency to initiate insulin to overcome this issue [12]. More than 50% of patients with DKD stages 4 and 5 have been reported to be on insulin therapy [13]. Exogenous insulin is primarily metabolized by kidney (30–80%), unlike by liver in non-diabetes individuals. Owing to the high molecular weight (5734 Da), around 65% of insulin is filtered in glomerulus and then metabolized in the proximal tubular cells [2]. About 35% of insulin diffuses to the contraluminal tubular membrane from post glomerular peritubular vessels of the proximal tubular cell, especially from the distal half of the nephron, where it is also degraded [9]. Different types of insulin-basal, bolus/prandial, premix and basal-bolus have been implicated in the management of DKD.

Multiple landmark trials have reported that intensive treatment of DM reduces the incidence of nephropathy and albuminuria and improves eGFR rate [14]. The Diabetes Control and Complications Trial (DCCT) and The Epidemiology of Diabetes Interventions and Complications (EDIC) study has established that intensive insulin therapy in type 1 DM (T1DM) patients was associated with reduction in nephropathy by 43% and 50%, respectively [15,16]. Similar benefits in type 2 DM (T2DM) were observed in the United Kingdom Prospective Diabetes Study (UKPDS) and the Veterans Affairs Diabetes Trial (VADT), where the risk reduction for microvascular complication was 24% and 37%, respectively [17,18]. Intensive glycaemic control in Action in Diabetes and Vascular Disease (ADVANCE) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) study has shown 21% and 32% reduction in the incidence of nephropathy, respectively [19,20]. Besides this, Steno-2 study had also demonstrated 60% reduction in the incidence of microalbuminuria in T2DM subjects, with intensified intervention [21].

The requirement of insulin shows a biphasic course in patients with renal disease and diabetes. In the beginning, insulin resistance deteriorates the glucose control; thereby

more insulin is needed to achieve glycaemic control [2]. When GFR reaches less than 20 mL/min, clearance is markedly reduced; as a result, the half-life of insulin increases and overall requirement declines. The reduction in insulin requirements is similar in type 1 and type 2 diabetes patients and is not affected by the residual insulin secretion in patients with T2DM [2,9]. The reduction in insulin clearance along with decreased renal gluconeogenesis by reduced kidney mass, impaired epinephrine release due to autonomic neuropathy, concurrent hepatic disease, decreased caloric intake, and deranged metabolic pathways (including altered metabolism of medications) might increases the risk of hypoglycaemia in patients with reduced eGFR [2,22]. The treatment modality and choice of insulin also influences the hypoglycaemic episode [23].

Except few studies, there is no comprehensive guidance established to summarize the insulin doses and its modification in CKD. In the need of developing a consensus, the expert group discussed the insulin dose modifications (titration and dosing) in various stages of CKD in the light of existing evidence and their clinical practice.

2. Methods

The evidence for the recommendations were assimilated from medical literature with the help of a systematic review of prime articles which included clinical studies, review articles and key guidelines on CKD. The above evidence was reviewed and analysed by the panel of doctors at the National Insulin Summit, held in Delhi on 20 August 2016. The recommendations were discussed by the expert panel which consisted of endocrinologists, physicians and key opinion leaders from various parts of India. The panel reviewed and debated each topic and arrived at the recommendations. The panel also discussed about the possible ways of individualizing the recommendations, keeping the local needs and essentialities in mind. The panel's lists of recommendations were used to build the consensus document and the draft of the same was circulated to all the participants for feedback and suggestions.

2.1. *Grading system*

The current consensus guidelines have been developed in accordance to the American Association of Clinical Endocrinologists (AACE) protocol for standardised production of clinical practice guidelines. Recommendations are organised by topic and are assigned evidence level (EL) ratings on the basis of the quality of supporting evidence all of which have also been rated for strength. Recommendations are based on clinical importance and graded as A (strongly recommend), B (intermediate), C (weak) and D (not evidence based), those are coupled by four intuitive levels of evidence: 1,2,3,4. They have been positioned on the basis of available evidence to be used for grading recommendations as follows.

"1": Meta-analysis of randomised controlled trials, randomized controlled trials
"2": Meta-analysis of nonrandomised prospective or case-controlled trials, nonrandomised controlled trial, prospective cohort study, retrospective case-control study
"3": Cross-sectional study, surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modelling of database), consecutive case series, single case reports
"4": No evidence (theory, opinion, consensus, review, or preclinical study)

3. Dosing, titration and dose estimation of insulin in CKD

Dosing and titration of insulin involves titration of insulin and insulin dose adjustment in CKD patients with different stages.

3.1. *Current place in guidelines/recommendations*

Kidney Disease Outcomes Quality Initiative (KDOQI) 2012 guideline does not provide any specific recommendation for insulin (prandial and basal) dose adjustment in patients with CKD stages 3,4 and 5. The guideline does not mention about premix or basal-bolus as there is not enough evidence of its use in CKD stages 3–5 [14]. Moreover, recent guidelines published by American Diabetes Association (ADA) and Canadian Diabetes Association (CDA) also does not provide any recommendations on the use of insulin in CKD patients with diabetes [24].

All available insulin preparations can be used, however, the insulin type, dose and administration must be tailored to each patient to achieve glycaemic control but, limit hypoglycaemia.

3.2. *Approved pack insert on dosing and titration*

Most approved pack inserts recommend careful glucose monitoring and dose adjustment of insulin in patient with renal impairment. No pack insert provides titration algorithm of insulin in patients with renal insufficiency.

3.3. *Published Scientific evidence*

Prandial insulin analogues have been reported to have a lesser risk of hypoglycaemia and better postprandial glucose (PPG) control than human insulin in CKD [9,25,26].

Various insulin analogues have been investigated in cases of renal impairment. Of prandial insulins, lispro (ILis) and glulisine (IGlu) significantly suppressed postprandial (PP) hyperglycaemia as compared to regular insulin [27,28]. There was no statistically significant difference in insulin aspart (IAsp) doses across different stages of eGFR (<60 mL/min, 60–80 mL/min, >90 mL/min), while there was a reduction in ILis and human insulin dose in patients with eGFR < 60 mL/min [29]. In addition, no change in the PK of IGlu and IAsp was observed in T2DM patients with severe renal failure [26,28].

Among basal insulins, insulin glargine (IGlar) appears to be safe and effective with rapid HbA1c reduction, stable half-life and longer duration of action in patients with renal failure [30]. Kulozik and Hasslacher demonstrated the need for dose reduction, for both IGlar and insulin detemir (IDet), across different stages of eGFR [29]. The dose requirement of IDet and IGlar was shown to be reduced up to 27% and 30% in patients with GFR < 60 mL/min. Moreover, insulin degludec (IDeg) did not reveal any significant difference in the absorption or

Table 1 – Summary of studies of various insulin analogues in patients with renal impairment.

Author (year)	Study design	Objectives	Patient population (Treatment arm)	Outcome
Prandial insulin				
Insulin Aspart (IAsp)				
Holmes et al. [26]	Prospective study (PK trial)	To assess the effects of renal impairment (creatinine clearance), on the PK of IAsp	T1DM (HbA1c $\leq$11%, FBG >4.44 and <8.33 mmol/L) since 2 years, with varying degrees of renal impairment (normal, $n = 6$ vs. mild renal impairment, $n = 7$ moderate renal impairments, $n = 3$ severe renal impairments, $n = 2$)	• No linear correlation exists between PK parameter and creatinine clearance in patients with varying degrees of renal failure
Insulin lispro (ILis)				
Ruggenenti et al. [27]	Randomized crossover study	To assess renal and metabolic responses to regular and lispro insulin (0.1 units/kg body weight) in T2DM patients with macroalbuminuria	11 Patients on continued treatment with OAD agents and/or insulin for at least 1 year, who had a serum creatinine <2.0 mg/dl and an albuminuria persistently $\geq$ 200 μg/min in two of the three urinary collections for at least 6 months	• Significantly lower PPG with insulin lispro (278 ± 16 vs. 240 ± 16 mg/dl, $p \leq 0.01$) and AUC (79,381 ± 19,237 vs. 72,810 ± 16,211 mg/dl per min, $p < 0,05$) than regular insulin injection, respectively
Aisenpreis et al. [34]	Prospective study (PK study)	To see whether insulin lispro facilitated blood glucose control in HD patients with DM	Two T1DM and six type T2DM patients participated in this study	• Lispro showed a more rapid absorption (maximum peak 30 vs. 51 min), shorter absorption $t_{1/2}$ (12 vs. 32 min), higher Cmax (146 vs. 88 mU/mL) and rapid reduction in serum glucose (20 min vs. 40 min) than regular human insulin, respectively
Czock et al. [35]	Crossover (PK Study)	To study the PK and PD of insulin lispro in renal failure patients	8 patients with DM on long-term HD received an individualized dose of regular insulin or insulin lispro in a crossover design	• Plasma insulin concentrations increased faster (tmax 20 vs 40 min, $p = 0.01$) and were higher (Cmax/D 13.6 vs 6.1 microU/mL/U, $p = 0.01$) after insulin lispro compared to regular insulin • Trend to reduce BG earlier was observed with insulin lispro (120 vs 210 min, $p > 0.05$)

Table 1 – (*continued*)

Author (year)	Study design	Objectives	Patient population (Treatment arm)	Outcome
Rave et al. [36]	Double-blind, two-way crossover	To quantify PK and PD properties of regular insulin and insulin lispro in T1DM patients with and without overt diabetic nephropathy	12 T1DM patients with overt diabetic nephropathy (proteinuria > 500 mg/24 h and/or serum creatinine >1.5 mg/dl) vs. control group of 12 T1DM patients with normal renal function	• Higher peak plasma free insulin levels were reported with insulin lispro (359 vs. 254 pmol/l) • Time to maximal insulin concentrations (85 vs. 99 min) were shorter than regular insulin
Insulin Glulisine (IGlu)				
Urata et al. [28]	Prospective study	To compare the efficacy and safety of IGlu over regular insulin in patients with T2DM and severe renal insufficiency	18 patients with T2DM and a mean eGFR of 13.2 mL/min/1.73 m^2 (5.8–27.6), which corresponds to stage 4–5 CKD	• IGlu effectively suppressed postprandial hyperglycemia, whereas regular insulin caused a prolonged hypoglycemic action
Basal insulin				
Insulin Glargine (IGlar)				
Niafar et al. [30]	Pilot multi-center clinical trial	To determine the safety and efficacy of IGlar in T2DM patients with diabetic nephropathy	89 subjects with T2DM who had diabetic nephropathy (mean GFR 34.1 ± 11.5 mL/min) were included in the study	• Significant reduction in HbA1c (from 8.4% ± 1.6 to 7.7% ± 1.2; $p < 0.001$) observed at the end of 4 months; $p < 0.001$) • Only mild symptomatic hypoglycemia (12.5%) reported
Insulin detemir (IDet)				
Kulozik & Hasslacher, [29]	Observational study	To identify potential differences in the requirements of human insulin and various insulin analogues in patients with T2DM and renal dysfunction	346 patients with T1DM were assessed for insulin requirements	29.7% lower insulin dosage in IGlar-treated patients and 27.3% lower in IDet-treated patients at eGFR < 60 mL/min compared with >90 mL/min. Dosage of lispro was 32.6% lower at eGFR < 60 mL/min than at >90 mL/min No association observed in requirements of IAsp with the eGFR

(*continued on next page*)

Table 1 – (continued)

Author (year)	Study design	Objectives	Patient population (Treatment arm)	Outcome
Insulin degludec (IDeg)				
Kiss et al. [31]	Single-center, single-dose, open-label, parallel-group trial	To evaluate the PK of insulin IDeg in subjects with normal, mild, moderate or severe renal dysfunction; or ESRD undergoing HD	30 subjects (n = 6 per group) received a single subcutaneous dose (0.4 U/kg) of IDeg	No significant differences in absorption or release profiles observed when compared to individuals with normal renal function
Basal-bolus insulin				
Glargine + Glulisine				
Baldwin et al. [32]	Multicenter, prospective, randomized trial	To compare two weight-based doses of insulin IGlar and IGlu for inpatients with T2DM and renal insufficiency	107 T2DM subjects were initiated to compare the efficacy of OD IGlar and TID IGlu at 0.5 vs. 0.25 units/kg/day	Reduction of initial IGlar/IGlu insulin weight-based dosing reduced the frequency of hypoglycemia by 50%

AUC: Area under curve; BG: Blood glucose; CKD: Chronic kidney disease; CRF: Chronic renal failure; DM: Diabetes mellitus; ESRD: End stage renal disease; FBG: Fasting blood glucose; eGFR: Estimated glomerular filtration rate; HD: Haemodialysis; ICT: Intensified conventional insulin treatment; OAD: Oral antidiabetic drug; OD: Once daily; PD: Pharmacodynamics; PK: Pharmacokinetics; PPG: Postprandial glucose; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; TID: three-times daily.

clearance in subjects with renal impairment when compared to individuals with normal kidney function [31].

There is no published evidence related to the use of premix insulin in CKD patients. In a prospective randomized trial, two weight-based dosing regimen (once-daily IGlar and three-times daily IGlu at 0.5 vs. 0.25 units/kg/day) were evaluated in 107 T2DM patients with GFR < 45 mL/min/1.73 m.^{2} Despite similar glycaemic control achieved with either of the doses, twice as many subjects with the higher weight-based insulin experienced hypoglycaemia compared with those who received 0.25 units/kg/day. This study further provided evidence for the benefit of dose reduction in inpatient subjects with T2DM and renal insufficiency [32].

Furthermore, based on the recommendations on the algorithm developed by the Duke University Medical Center Glycaemic Safety Committee, prompt adjustments with reduction of 30%, 50% and 60% are often necessary in total daily dose (TDD) depending on the CKD stages 3, 4 and 5 respectively. However, no dose modification was suggested in patients with CKD stages 1 & 2 [33]. Summary of published evidence from several clinical trials, observational and case studies which evaluated different insulin analogues in diabetes with impaired renal function is provided in Table 1.

Expert group recommendation 1: Dosing and Titration of Insulins in CKD

Recommendation on Dose Titration

GFR (mL/min/1.73 m^2)	% Reduction of TDD
>60	No Reduction
60–15	25%
<15	50%

Expert group recommendation 2: Dose Estimation of Insulins in CKD according to the body weight

Recommendation on Dose Estimation

GFR (mL/min/1.73 m^2)	Insulin Dose (Units/kg/Day)	
	Type 1 DM	Type 2 DM
>60	1.0	0.5
60–15	0.75	0.3–0.4
<15	0.5	0.25

CKD: Chronic kidney disease; DM: Diabetes mellitus; GFR: Glomerulus filtration rate; TDD: Total daily dose.

4. Glycaemic targets in CKD

4.1. *Current place in guidelines/recommendations*

ADA recommends target glycated haemoglobin (HbA1c) for diabetes control as <7%. It also recommends both higher (<8%) or stricter (<6.5%) HbA1c goals for certain populations [24]. The KDOQI 2007 guideline for diabetes and CKD recommends a target HbA1c of <7.0%, which was further revised to ~7.0% in their updated 2012 guidelines [14]. Customization of this general target is based on the patient characteristics, with tighter control. The 2012 KDOQI guideline recommends the HbA1c target of ~7.0% to prevent or delay progression of microvascular complications of diabetes, including DKD

Table 2 – Summary of published evidence evaluated the proposed glycaemic control parameters for diabetic patients with renal disease.

Author (year)	Study objectives	Subjects	Outcome
Suzuki and Arakawa [38]	To study the relationships among the clinical course and features including DM treatment	725 diabetic subjects maintained on HD	For patients less than 70 years old, the survival period was longer in patients with serum HbA1c values of less than 7.5%, compared to those with greater than 7.5%
Yu et al. [39]	To evaluate the correlation between pre-dialysis glycemic control and clinical outcomes	60 T2DM subjects maintained on CAPD	Predialysis glycemic control [Exp (coef) = 0.42, $p = 0.0092$] had a significantly better survival
Wu et al. [40]	To evaluate the correlation between the pre-dialysis glycaemic control and the clinical outcome	137 T2DM patients maintained on HD	The 1-year (94.5% vs 80%), 3-year (82.9% vs. 58.1%) and 5-year (75.8 vs. 21.8%) cumulative rates of survival were lower in the patients with poor glycaemic control as compared to those with good glycaemic control
Wu et al. [41]	To evaluate the impact of pre-dialysis glycemic control on clinical outcomes	101 T2DM patients maintained on CAPD	Pre-dialysis glycemic control [exponent (coefficient) = 0.420, $p < 0.01$] had significant influence on patient survival
Morioka et al. [42]	To investigate the impact of glycemic control on the survival of subjects with diabetes and ESRD	150 diabetic subject on HD	The patients with HbA1c < 7.5% had better survival than those with ≥7.5% ($P = 0.008$)
Park et al. [43]	To evaluate the effect of HbA1c on mortality of patients on dialysis	1239 diabetic patients, of which 873 patients received HD and 366 PD	HbA1c ≥ 8% was a predictor of mortality in age <55 (HR, 4.3; 95% CI, 1.78–10.41; $p = 0.001$) and age 55–64 groups (HR, 3.3; 95%CI, 1.56–7.05; $p = 0.002$), but not in age ≥65 group
Hill et al. [44]	To investigate the association between HbA1c level and mortality risk in diabetic patients on HD	A meta-analysis of 10 studies (83,684 participants receiving HD)	Patients with baseline HbA1c levels ≥8.5% had increased mortality (7 studies; HR, 1.14; 95% CI, 1.09–1.19) compared with patients with HbA1c levels of 6.5–7.4%
Shurraw et al. [45]	To study whether lower HbA1c improves outcomes in people with DM and CKD	23,296 DM patients with an eGFR < 60.0 mL/min/1.73 m^2	Increases in the risk of mortality was apparent at HbA1c levels lower than 6.5% and higher than 8.0%
Ricks et al. (2012) [46]	To examine the mortality predictability of HbA1C and random serum glucose patients with diabetes receiving MHD	54,757 subjects with diabetes and MHD patients	HbA1c ≥ 8% or serum glucose ≥ 200 mg/dL were associated with high all-cause and cardiovascular death. Very low glycemic levels were also associated with high mortality risk
Ramirez et al. [47]	To study the relationship between A1c levels and mortality in an international prospective cohort study of HD patients	9201 HD patients with T1DM or T2DM	HbA1c between 7 and 7.9%, carries least risk of all-cause and cardiovascular death, which increases for either lower or higher HbA1c levels
Alder et al. [48]	To investigate an association, in individuals with diabetes, between glycemia measured at the start of dialysis and subsequent mortality	3157 patients with diabetes receiving RRT	No association was reported between HbA1c and patient's death who are ≥60 years of age. Patients who started dialysis at a younger age (<60 years old) had poorer survival with HbA1c > 8.5%

CAPD: Continuous ambulatory peritoneal dialysis; CKD: Chronic kidney disease; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; HR: Hazards ratio; HD: Haemodialysis; MHD: Maintenance hemodialysis; PD: Peritoneal dialysis; RRT: Renal replacement therapy T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

(1A). They further recommend to not treat to an HbA1c target of <7.0% in patients at risk of hypoglycaemia (1B). Lastly, the target HbA1c is recommended be extended above 7.0% in individuals with co-morbidities or limited life expectancy and risk of hypoglycaemia (2C) [14].

4.2. *Approved pack insert on glycaemic targets*

No pack insert provides any glycaemic targets in patients with renal insufficiency.

4.3. *Published Scientific evidence*

There is little evidence available regarding the effect of optimal glycaemic control on renal function and morbidity and mortality in diabetes patients during pre-dialysis or dialysis therapy. HbA1c between 7 and 8% appear to be correlated with the best survival rates in DKD patients [37]. Few studies have recommended pre-dialysis HbA1c <7%, which improve long term outcomes during the dialysis period in DKD patients [9]. Furthermore, few studies have evaluated the optimal glycaemic control in diabetes dialysis patients and recommended HbA1c < 7.5–8.0%, fasting blood glucose < 140 mg/dl and 2-h postprandial blood glucose < 200 mg/dl to improve patient outcome [9]. Summary of published evidence which evaluated the proposed glycaemic control parameters for diabetes patients with renal disease is provided in Table 2.

Expert group recommendation 3: Glycaemic Targets in CKD
Recommendation on Glycaemic Targets

GFR (mL/min/1.73 m^2)	HbA1c Target[a]
>60	<7%[a]
<60	7.0–8.5%[a]

CKD: Chronic kidney disease; GFR: Glomerular filtration rate.
[a] Consider a lower HbA1c if patient does not develop hypoglycaemia.

5. Blood glucose monitoring in CKD

5.1. *Current place in guidelines/recommendations*

The 2007 KDOQI working group suggested the monitoring of glycaemic control in accordance with the general standards recommended by the ADA in DKD patients. The frequency of self-monitoring of blood glucose (SMBG) should be 3 or more times daily (before meals and at bedtime) in patients receiving multiple insulin injections. Postprandial SMBG testing, to achieve postprandial glycaemic goals, are also suggested in patients using rapid insulin injections which helps in adjusting the dose-meal calculation [49].

5.2. *Published scientific evidence*

One of the biggest challenge in achieving strict glycaemic targets in patients with CKD and diabetes is hypoglycaemia. Iyer and Tenenberg, in a recent review, recommended prudent blood glucose monitoring in all hospitalized patients with known diabetes with or without CKD. In addition, blood glucose monitoring every 4–6 h is recommended in patients with no oral intake or on continuous enteral or parenteral nutrition [50].

The optimal frequency of SMBG has not been reported in the published literatures, but should be sufficient to reach glycaemic goals. Fingerstick blood glucose monitoring is recommended, in patients on scheduled diets, before meals and at bedtime [50]. Nevertheless, the frequency of self-monitoring must be individualized and adapted as per the clinical conditions of the patient [51].

Continuous glucose monitoring systems (CGMS) have been validated as a reliable and accurate measure of blood glucose in uremic patients on dialysis and enable better glucose control by providing real-time glucose measurements [52].

In a pilot study, Yeoh et al. observed no difference between CGM and SMBG over 3 months in improving glycaemic control in stage 3 DKD patients. At 3 months, there was a significant improvement in HbA1c from baseline 9.9 ± 1.2 vs 9.0 ± 1.5% ($p < 0.001$). HbA1c reduced from (9.8 ± 1.2 to 8.8 ± 1.8%, $p = 0.009$) in the CGM group and from (9.9 ± 1.3 to 9.1 ± 1.1%, $p = 0.007$) in the SMBG group with no difference between the groups ($p = 0.869$) [53].

Self-monitoring does not interfere with monitoring in patients with diabetes and CKD, however, patient must follow the continued practice of DM education and should be instructed regarding the proper use and benefits of SMBG [50,51].

Expert group recommendation 4: Blood Glucose Monitoring in CKD
Recommendation on Blood Glucose Monitoring

Stage of CKD	Description	GFR (mL/min/1.73 m^2)	Recommendation
1	Kidney damage[a] with normal or increased GFR	≥90	To be done as per insulin regimen (from only fasting to 4 times a day)
2	Kidney damage[a] with mildly decreased GFR	60–89	
3	Moderately decreased GFR	30–59	
4	Severely decreased GFR	15–29	
5	Kidney failure	<15 or dialysis	

CKD: Chronic kidney disease; GFR: Glomerular filtration rate.
[a] SMBG should be the preferred choice. If patients can afford, CGMS may be considered.

6. Conclusion

The management of the patients with DKD, preferably treated with insulin, calls for close collaboration between the multidisciplinary team consisting of nephrologists, endocrinologists, nutritionists, and nurses. Despite, insulin being considered as the most effective therapeutic regimen in DKD patients, its prescription need frequent reassessment for individualization, adjustment and titration of doses in accordance with the eGFR. In addition, special attention should be given to the intensification of glycaemic control along with monitoring of hypoglycaemia. Individualized approach of appropriate glycaemic targets with the aim of reducing the occurrence of hypoglycaemia should be practiced. The consensus based recommendations described are based on the existing guidelines on insulin regimen and adapted from algorithms used in several clinical trials and clinical observations can be further simplified as follows:

- Insulin doses in CKD to be reduced with lower eGFR levels.
- Insulin doses in CKD can be estimated according to body weight.
- The optimal glycaemic target should also be determined as per the GFR value.
- Blood glucose monitoring should be done as per the severity of kidney disease.
- SMBG should be the preferred choice, however, CGMS may be considered if patients can afford.

These recommendations are anticipated to provide guidance to the clinicians and specialists in treating DKD patients.

The strength of the current consensus is that it has been developed based upon clinical experience in relation with Indian context while giving due consideration to recommendations from globally acceptable guidelines and published evidences.

The limitations of the consensus emanate from the fact that there is paucity of published literature which has studied the role of insulin in DKD patients. The primary purpose of most of the published trials was not to evaluate the appropriate glycaemic control in patients with diabetes and more advanced CKD. Hence, interpretation of the algorithm merit in those cases is somewhat difficult and has to rely on cross trial comparisons.

We hope that these consensus recommendations will be a useful reference tool for physicians and that their impact will be validated through observational research in real-life practice, involving large number of physicians and in the setting of routine outpatient care of T2DM in India.

7. Recommendations for further research

Multipronged strategies with novel investigational agents aiming newly identified mechanistic pathways, such as inflammation, fibrosis, and other processes, need to be established in CKD patients with diabetes. Further trials evaluating the intensified therapy targeted at traditional risk factors (BP and dyslipidaemia), along with CKD complications such as bone mineral disorder, anaemia, and volume overload, would be of value [54]. More studies are required to evaluate the appropriate frequency of screening (eGFR and microalbuminuria) along with implementing routine kidney biopsy and its effect on disease outcomes [55]. In addition, glycaemic profile using HbA1c has shown many limitations including reduced red cell survival time, hemoglobin modifications and mechanical destruction of red blood cells on dialysis [56]. Hence the role of CGMS to improve patient outcome in DKD patients need to be established. Furthermore, more evidence is are needed with novel glucose-lowering agents that are not associated with hypoglycaemia.

Other important areas of research include point-of-care strategies, dedicated risk assessment and safety education programs along with implementation of self-monitoring tools. There is further need for more research in vulnerable populations such as young adolescents, heterogeneous populations and at-risk populations who present with unique management issues and in whom DKD is over-represented.

Conflict of interest

The authors have no conflicts of interest to report.

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